

**IN THE UNITED STATES
PATENT AND TRADEMARK OFFICE**

Appl. No. : 10/596,920
Applicants : Ties VAN BOMMEL et al.
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Examiner : SCHLIENTZ, Leah H.

Atty. Docket : DE040020

Title: ULTRASOUND CONTRAST AGENTS FOR
MOLECULAR IMAGING

APPEAL BRIEF

Mail Stop **Appeal Brief - Patents**
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

In response to the FINAL Office Action dated 24 February 2010 and the Advisory Action of 4 May 2010, and in support of the Notice of Appeal filed on 24 May 2010, Applicants hereby respectfully submit this Appeal Brief.

REAL PARTY IN INTEREST

Koninklijke Philips Electronics N.V. owns all of the rights in the above-identified U.S. patent application.

RELATED APPEALS AND INTERFERENCES

There are no other appeals or interferences related to this application or to any related application, nor will the disposition of this case affect, or be affected by, any other application directly or indirectly.

STATUS OF CLAIMS

Claims 1-14 are canceled.

Claims 15-33 are pending in the application.

Claims 15-33 all stand rejected.

Accordingly, the claims on appeal are claims 15-33.

STATUS OF AMENDMENTS

There are no pending amendments with respect to this application. The last Amendment to this application was filed on 26 April 2010 and entered by the Examiner by the Advisory Action dated 4 May 2010.

SUMMARY OF CLAIMED SUBJECT MATTER

The present invention is directed to a method of ultrasound molecular imaging of tissue using contrast agents.¹

Accordingly, as broadly recited in claim 15, a method of diagnosis comprises: administering a contrast agent (page 4, lines 7-9) comprising solid metal nano-particles (page 2, lines 26-27; page 5, lines 21-27) having an acoustic impedance above 35×10^5 g/cm²s (page 3, lines 3-4; page 5, lines 8-10) to an animal or human subject (page 9, lines 6-10); applying an ultrasonic sound wave (page 3, line 27 – page 4, line 1; page 7, lines 27-31; page 9, lines 6-10) to the animal or human subject; and receiving ultrasound sound wave reflections produced by the ultrasonic wave in the animal or human subject, including ultrasound sound wave reflections from the nano-particles (page 2, lines 30-31; page 3, line 27 – page 4, line 1; page 12, lines 10-17).

As broadly recited in claim 16, a method of imaging an isolated tissue sample

¹ In the description to follow, citations to various reference numerals, figures, and corresponding text in the specification are provided solely to comply with Patent Office rules. It should be understood that these reference numerals, figures, and text are exemplary in nature, and not in any way limiting of the true scope of the claims. It would therefore be improper to import anything into any of the claims simply on the basis of **exemplary** language that is provided here only under the obligation to satisfy Patent Office rules for maintaining an Appeal.

or organ (page 7, lines 1-2; page 9, lines 18-22) comprises: administering a contrast agent (page 4, lines 10-11) comprising solid metal nano-particles (page 2, lines 26-27; page 5, lines 21-27) having an acoustic impedance above 35×10^5 g/cm²s (page 3, lines 3-4; page 5, lines 8-10) to said tissue sample or organ; applying an ultrasonic sound wave to the sample or organ (page 3, line 27 – page 4, line 1; page 7, lines 27-31; page 9, lines 18-22); and receiving ultrasound sound wave reflections produced by the ultrasonic wave in the sample or organ, including ultrasound sound wave reflections from the nano-particles (page 2, lines 30-31; page 3, line 27 – page 4, line 1; page 12, lines 10-17).

As further featured in claims 30 and 31, the metal is rhenium (page 5, lines 12-15).

GROUND OF REJECTION TO BE REVIEWED ON APPEAL

The grounds of rejection to be reviewed on Appeal are: (1) the rejections of claims 15-29, 32 and 33 under 35 U.S.C. § 103 over Hainfeld U.S. Patent 6,818,199 ("Hainfeld I") in view of West U.S. Patent Application Publication 2002/0103517 ("West"); (2) the rejections of claims 15-23, 25-28 and 32-33 under 35 U.S.C. § 103 over Bekeredjian; and (3) the rejections of claims 15-33 under 35 U.S.C. § 103 over Hainfeld I in view of West and further in view of Hainfeld U.S. patent Application Publication 2005/0020869 ("Hainfeld II").

ARGUMENTS

(1) Claims 15-29, 32 & 33 Are Patentable

Under 35 U.S.C. § 103 Over Hainfeld I & West

Claim 15

Among other things, the method of claim 15 includes receiving ultrasound sound wave reflections produced by an ultrasonic wave in an animal or human subject, including ultrasound sound wave reflections from solid metal nano-particles having an acoustic impedance above 35×10^5 g/cm²s.

Applicants respectfully submit that no combination of the teachings of Hainfeld I and West would produce a method including this combination of features.

The Examiner does not cite anything in Hainfeld I or West that teaches such a combination of features, and specifically the reception of ultrasound wave reflections from solid metal nano-particles.

Absent a teaching of this feature, the cited combination of Hainfeld I and West can not produce the method of claim 15.

The Office Action states that it would have been “*inherent*” in “*Hainfeld and/or West*” to receive ultrasound sound wave reflections produced by an ultrasonic wave in an animal or human subject, including ultrasound sound wave reflections from solid metal nano-particles having an acoustic impedance above 35×10^5 g/cm²s.

Applicants respectfully disagree.

M.P.E.P. § 2112(IV) provides that:

“The fact that a certain result or characteristic may occur or be present in the prior art is not sufficient to establish the inherency of that result or characteristic. In re Rijckaert, 9 F.3d 1531, 1534, 28 USPQ2d 1955, 1957 (Fed. Cir. 1993) (reversed rejection because inherency was based on what would result due to optimization of conditions, not what was necessarily present in the prior art); In re Oelrich, 666 F.2d 578, 581-82, 212 USPQ 323, 326 (CCPA 1981). “To establish inherency, the extrinsic evidence ‘must make clear that the missing descriptive matter is necessarily present’ in the thing described in the reference, and that it would be so recognized by persons of ordinary skill. Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient.” In re Robertson, 169 F.3d 743, 745, 49 USPQ2d 1949, 1950-51 (Fed. Cir. 1999) (citations omitted).”

(emphasis added).

Here, Applicants respectfully submit that the Examiner has failed to meet the burden of showing that a feature of receiving ultrasound sound wave reflections

produced by an ultrasonic wave in an animal or human subject, including ultrasound sound wave reflections from solid metal nano-particles having an acoustic impedance above $35 \times 10^5 \text{ g/cm}^2\text{s}$ is necessarily present in the teachings of Hainfeld I or West or any proper combination thereof.

Meanwhile, the Examiner cites col. 19, lines 10-15 of Hainfeld I as supposedly teaching the use of metal nano-particles in acoustic imaging.

Applicants respectfully disagree. The cited text explicitly lists forms of electromagnetic radiation. In fact, Hainfeld I uses the term electromagnetic radiation twice in the cited sentence, at the beginning and again at the end.

This makes sense, as Hainfeld I's disclosure is totally focused on exploiting the electromagnetic absorption properties of its metal nano-particles (see, e.g., col. 6, lines 47-49) for X-ray imaging. Throughout Hainfeld I's disclosure, the discussion always pertains to some form of electromagnetic radiation, mostly X-rays. There is no mention of any form of high-contrast acoustic imaging, or of selecting and employing nano-particles that would have good properties for high-contrast acoustic imaging, or that solid metal nano-particles having an acoustic impedance above $35 \times 10^5 \text{ g/cm}^2\text{s}$ could or should be effectively employed for high-contrast acoustic imaging.

One can only conclude that by the plain language of col. 19, lines 10-15, and the context presented by the remainder of Hainfeld I's disclosure, that Hainfeld I is referring to low frequency electromagnetic waves.

Furthermore, there is no disclosure or suggestion in Hainfeld I of the acoustic properties (e.g., acoustic impedance) of the nano-particles that Hainfeld I discusses, or any suggestion of what acoustic properties would render nano-particles beneficial for acoustic imaging. Other than the cited sentence from column 19, which Applicants respectfully submit pertains to low-frequency electromagnetic waves, nothing else in Hainfeld I discloses or suggests that Hainfeld I's nano-particles are suitable for, or should be employed with, high-contrast acoustic imaging techniques.

So it is not reasonable to interpret the cited language in col. 19 of Hainfeld I as pertaining to acoustic waves, and Hainfeld I does not "inherently" teach receiving ultrasound sound wave reflections from solid metal nano-particles having an acoustic

impedance above 35×10^5 g/cm²s (see M.P.E.P. § 2112(IV) cited above).

Furthermore, M.P.E.P. § 2121.01 provides that the teachings from the cited reference(s) must provide an enabling disclosure of the desired subject matter; mere naming or description of the subject matter is insufficient.

Here, Hainfeld I does not enable receiving ultrasound wave reflections produced by an ultrasonic sound wave in an animal or human subject, including ultrasound wave reflections from solid metal nano-particles having an acoustic impedance above 35×10^5 g/cm²s, as Hainfeld I makes no mention of any acoustic properties of its nano-particles, and does not mention or give any example of receiving ultrasound sound wave reflections from its nano-particles.

Meanwhile, West is directed to methods of localized heating of nanoshells and imaging based on such heated nanoshells (e.g., near-IR imaging – see, e.g., paragraph [0062]). Toward this end, West employs a number of radiation sources, including ultrasound, to heat its nanoshells, and this heat is then detected with near-IR imaging. So, West discloses, for example in claims 12, 15, 33 and 34, that the radiation source for heating the nanoshells may include ultrasound, but West does not disclose that that the imaging is performed from ultrasound reflections from the nanoshells (as opposed to infrared reflections from the heated nanoshells, which West does disclose and claim).

So Applicants respectfully submit that receiving ultrasound sound wave reflections produced by an ultrasonic wave in an animal or human subject, including ultrasound sound wave reflections from solid metal nano-particles having an acoustic impedance above 35×10^5 g/cm²s, is not taught by, or inherent in Hainfeld and/or West.

Therefore, for at least these reasons, Applicants respectfully submit that no proper combination of Hainfeld I and West could produce the method of claim 15.

Applicants also traverse the proposed combination of Hainfeld I and West. The Examiner states that both Hainfeld I and West are directed to ultrasound. However, as explained above, Applicants respectfully submit that neither Hainfeld I nor West pertains to acoustic imaging, and there would have been no reason to apply West's teachings about *in vivo* use of its nanoshells for infrared imaging, with

Hainfeld I's method of enhancing the efficacy of electromagnetic radiation therapy using metal nano-particles.

Therefore, for at least these reasons, Applicants respectfully submit that claim 15 is patentable over Hainfeld I and West. Accordingly, Applicants respectfully request that the rejection of claim 15 over Hainfeld I and West be withdrawn

Claim 16

Among other things, the method of claim 16 includes receiving ultrasound sound wave reflections produced by an ultrasonic wave in a sample or organ, including ultrasound sound wave reflections from solid metal nano-particles having an acoustic impedance above 35×10^5 g/cm²s.

For similar reasons to those set forth above with respect to claim 15, Applicants respectfully submit that no combination of the teachings of Hainfeld I and West would produce a method including this combination of features.

Therefore, for at least these reasons, Applicants respectfully submit that claim 16 is patentable over Hainfeld I and West. Accordingly, Applicants respectfully request that the rejection of claim 16 over Hainfeld I and West be withdrawn.

Claims 17-29, 32 and 33

Claims 17-29, 32 and 33 depend variously from claims 15 and 16 and are deemed patentable over Hainfeld I and West for at least the reasons set forth above with respect to claims 15 and 16.

(2) Claims 15-23, 25-28 and 32-33 Are Patentable

Under 35 U.S.C. § 103 Over Bekeredjian

Claim 15

Among other things, the method of claim 15 includes administering a contrast agent comprising solid metal nano-particles having an acoustic impedance above 35×10^5 g/cm²s to an animal or human subject.

Applicants respectfully submit that Bekeredjian does not disclose or suggest administering **solid metal nano-particles having an acoustic impedance above 35×10^5 g/cm²s**. Instead, Bekeredjian discloses attaching gold colloids to the walls of microtubules, and administering the colloidal gold-bound microtubules as the contrast

agent.

Applicants respectfully submit that administering colloidal gold-bound microtubules is not administering solid metal nano-particles having an acoustic impedance above 35×10^5 g/cm²s.

In that regard, the Board's attention is drawn to the text at page 2, lines 18-25 of the present specification which discusses Bekeredjian's microtubules, and the text at page 5, lines 21-27 which discusses the claimed solid metal nano-particles.

Applicants respectfully submit that nothing in Bekeredjian suggests the administration of such solid metal nano-particles having an acoustic impedance above 35×10^5 g/cm²s as a contrast agent for acoustic imaging.

Therefore, for at least these reasons, Applicants respectfully submit that claim 15 is patentable over Bekeredjian. Accordingly, Applicants respectfully request that the rejection of claim 15 over Bekeredjian be withdrawn

Claim 16

Among other things, the method of claim 16 includes receiving ultrasound sound wave reflections produced by an ultrasonic wave in a sample or organ, including ultrasound sound wave reflections from solid metal nano-particles having an acoustic impedance above 35×10^5 g/cm²s.

For similar reasons to those set forth above with respect to claim 15, Applicants respectfully submit that claim 16 is patentable over Bekeredjian. Accordingly, Applicants respectfully request that the rejection of claim 16 over Bekeredjian be withdrawn.

Claims 17-23, 25-18, 32 and 33

Claims 17-23, 25-28, 32 and 33 depend variously from claims 15 and 16 and are deemed patentable over Bekeredjian for at least the reasons set forth above with respect to claims 15 and 16.

(3) Claims 15-33 Are Patentable

Under 35 U.S.C. § 103 Over Hainfeld I, West & Hainfeld II

Claim 15

Among other things, the method of claim 15 includes receiving ultrasound

sound wave reflections produced by an ultrasonic wave in an animal or human subject, including ultrasound sound wave reflections from solid metal nano-particles having an acoustic impedance above $35 \times 10^5 \text{ g/cm}^2\text{s}$.

Applicants respectfully submit that no combination of the teachings of Hainfeld I, West and Hainfeld II would produce a method including this combination of features.

The Examiner does not cite anything in Hainfeld I or West or Hainfeld II that teaches such a combination of features, and specifically the reception of such ultrasound wave reflections from such nano-particles.

The discussion on page 13 of the FINAL Office Action of 24 February 2010 of the rejection of claim 15 over Hainfeld I, West and Hainfeld II focuses on "rhenium" which is a feature of claims 30 and 31, but not claim 15. The Examiner does not explain how the rejection of claim 15 based on Hainfeld I, West and Hainfeld II is supposedly any different between the previous rejection of claim 15 over Hainfeld I and West. Lacking any specific information from the Examiner on the supposed applicability of Hainfeld II to claim 15, and given the statement that "*the rejection over Hainfeld '199 in view of West is applied as above,*" Applicants therefore respectfully traverse the rejection of claim 15 over Hainfeld I, West and Hainfeld II for the same reasons as set forth above with respect to the rejection of claim 15 over Hainfeld I and West.

Therefore, for at least these reasons, Applicants respectfully submit that claim 15 is patentable over Hainfeld I, West and Hainfeld II. Accordingly, Applicants respectfully request that the rejection of claim 15 over Hainfeld I, West and Hainfeld II be withdrawn

Claim 16

Among other things, the method of claim 16 includes receiving ultrasound sound wave reflections produced by an ultrasonic wave in a sample or organ, including ultrasound sound wave reflections from solid metal nano-particles having an acoustic impedance above $35 \times 10^5 \text{ g/cm}^2\text{s}$.

For similar reasons to those set forth above with respect to claim 15, Applicants respectfully submit that no combination of the teachings of Hainfeld I,

West and Hainfeld II would produce a method including this combination of features.

Therefore, for at least these reasons, Applicants respectfully submit that claim 16 is patentable over Hainfeld I, West and Hainfeld II. Accordingly, Applicants respectfully request that the rejection of claim 16 over Hainfeld I, West and Hainfeld II be withdrawn.

Claims 17-33

Claims 17- 33 depend variously from claims 15 and 16 and are deemed patentable over Hainfeld I, West and Hainfeld II for at least the reasons set forth above with respect to claims 15 and 16, and for the following additional reasons.

Claims 30 and 31

Among other things, the methods of claims 30 and 31 include receiving ultrasound sound wave reflections produced by an ultrasonic wave in an animal or human subject, including ultrasound sound wave reflections from solid rhenium nanoparticles having an acoustic impedance above $35 \times 10^5 \text{ g/cm}^2\text{s}$.

Applicants respectfully submit that Hainfeld I, West and Hainfeld II, taken alone or collectively, do not teach any method including such a combination of features.

It appears that the Examiner admits that Hainfeld I, West do not teach the use of such rhenium particles in ultrasonic imaging.

It appears that Hainfeld II is cited to supply this missing teaching.

In particular, the Examiner maintains that Hainfeld II teaches “*rhenium to be functionally equivalent to gold and other metal nanoparticles, including for interaction with forms of energy including ultrasound.*”

Applicants respectfully disagree. Hainfeld II is concerned with enhancing the effectiveness of electromagnetic radiation therapy – not imaging. Therefore, Hainfeld II is concerned with a particular characteristic of how its particles interact with electromagnetic radiation, namely the radiation absorption rate of the material. Hainfeld II does not mention anything about how its particles interact with acoustic radiation, for example the acoustic impedance of the particles.

Applicants respectfully submit that Hainfeld II does not teach or suggest the use of solid rhenium nano-particles in ultrasonic imaging. Instead, Hainfeld II only

teaches the use of nano-particles made from rhenium in a therapeutic application to enhance energy delivery to target tissue, for example via Compton scattering, the photoelectric effect, and pair production. Hainfeld II does not disclose or suggest the use of rhenium as an imaging contrast agent, and particularly does not disclose or suggest their use or suitability as an imaging contrast agent for acoustic imaging (e.g., ultrasonic sound waves).

Therefore, Applicants respectfully traverse the proposed combination of Hainfeld I, West and Hainfeld II and respectfully submit that any proper combination of Hainfeld I, West and Hainfeld II would not produce the methods of claims 30 & 31.

For all of the foregoing reasons, Applicants respectfully submit that the rejections of claims 15-33 are all in error. Therefore, Applicants respectfully request that that the Board reverse the rejections of claims 15-33, and the application be returned to the Examiner for further processing.

Respectfully submitted,

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CLAIMS APPENDIX

15. (Previously Presented) A method of diagnosis comprising:
administering a contrast agent comprising solid metal nano-particles having an acoustic impedance above $35.10^5 \text{ g/cm}^2\text{s}$ to an animal or human subject;
applying an ultrasonic sound wave to the animal or human subject; and
receiving ultrasound sound wave reflections produced by the ultrasonic wave in the animal or human subject, including ultrasound sound wave reflections from the nano-particles.

16. (Previously Presented) A method of imaging an isolated tissue sample or organ, comprising:
administering a contrast agent comprising solid metal nano-particles having an acoustic impedance above $35.10^5 \text{ g/cm}^2\text{s}$ to said tissue sample or organ;
applying an ultrasonic sound wave to the sample or organ; and
receiving ultrasound sound wave reflections produced by the ultrasonic wave in the sample or organ, including ultrasound sound wave reflections from the nano-particles.

17. (Previously Presented) The method of claim 15, wherein the contrasting agent has an acoustic impedance of above $50.10^5 \text{ g/cm}^2\text{s}$.

18. (Previously Presented) The method of claim 15, wherein the metal nano-particles have a diameter of between 1 nm and 100 nm.

19. (Previously Presented) The method of claim 15, wherein the metal nano-particles have a diameter of between 1 nm and 50 nm.

20. (Previously Presented) The method of claim 15, wherein the metal is non-magnetic.

21. (Previously Presented) The method of claim 15, wherein the metal is selected from the group consisting of gold, silver, platinum, palladium, tungsten or tantalum, rhenium, or a mixture thereof.

22. (Previously Presented) The method of claim 15, wherein the metal is a noble metal.

23. (Previously Presented) The method of claim 15, which further comprises one or more coatings.

24. (Previously Presented) The method of claim 23, wherein the coating comprises natural or synthetic carbohydrates, synthetic polyaminoacids, or physiologically tolerable synthetic polymers or derivatives thereof.

25. (Previously Presented) The method of claim 23, wherein the one or more coating comprises a therapeutic agent.

26. (Previously Presented) The method of claim 15, characterized in that one or more bio-target-specific molecules are attached to the surface of the metal particle.

27. (Previously Presented) The method of claim 26, wherein the bio-target-specific molecule recognizes a target which is selected from the group consisting of a cellular marker, a pathogen and a foreign and/or toxic agent.

28. (Previously Presented) The method of claim 26, wherein the bio-target-specific molecule is an antibody or a fragment thereof.

29. (Previously Presented) The method of claim 15, wherein administering the contrast agent comprises orally administering one of a tablet and a capsule including the contrast agent.

30. (Previously Presented) The method of claim 15, wherein the metal is rhenium.

31. (Previously Presented) The method of claim 16, wherein the metal is rhenium.

32. (Previously Presented) The method of claim 16, wherein the contrasting agent has an acoustic impedance of above $50.10^5 \text{ g/cm}^2\text{s}$.

33. (Previously Presented) The method of claim 16, wherein the metal is selected from the group consisting of gold, silver, platinum, palladium, tungsten or tantalum, rhenium, or a mixture thereof.

EVIDENCE APPENDIX

{None}

RELATED PROCEEDINGS APPENDIX

{None}